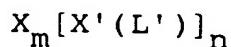


What is claimed:

1. An excipient for a metal chelate contrast agent, wherein said metal chelate contrast agent, M(L), comprises a metal ion complexed with  
 5 an organic ligand, which excipient has the formula



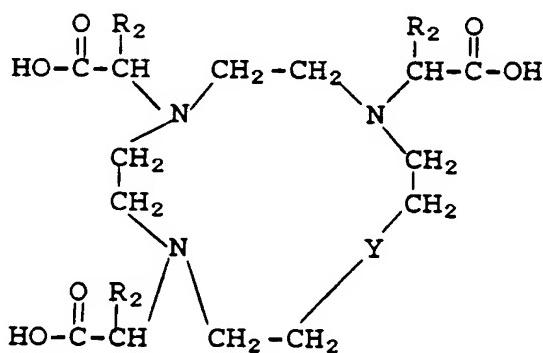
wherein X and X' are each independently selected  
 10 from calcium or zinc, L' is an organic ligand which may be L or another organic ligand which has a greater affinity for M than for calcium or zinc, and wherein m and n are each independently 1, 2 or 3.

15 2. The excipient of claim 1 wherein X = X'  
 = calcium.

20 3. The excipient of claim 1 wherein L and L' are independently selected from linear and macrocyclic polyaminopolycarboxylic acids and derivatives thereof.

4. The excipient of claim 1 wherein L and L' are independently selected from compounds of the formula

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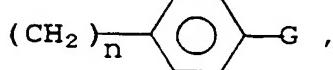
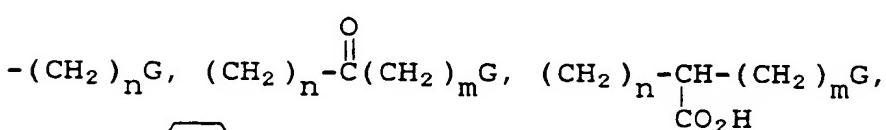
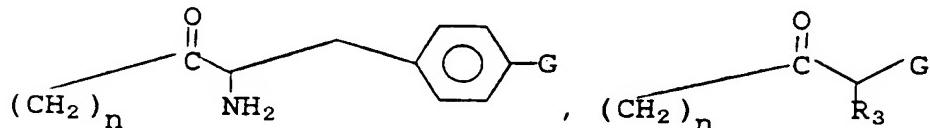


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wherein

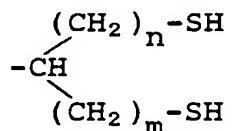
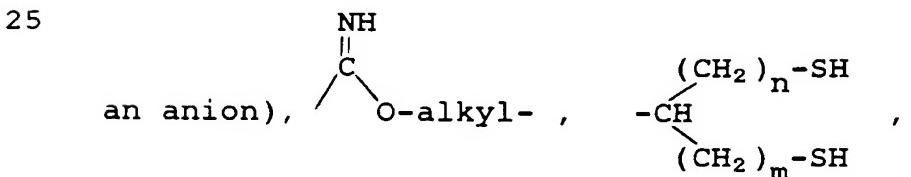
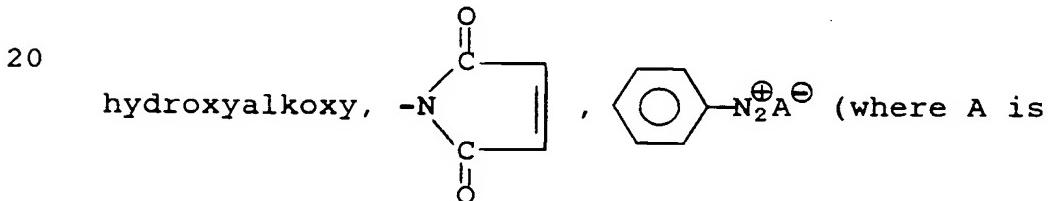
Y is oxygen or  $\begin{matrix} R_1 \\ | \\ -N- \end{matrix}$ ;

- 5      R<sub>1</sub> and R<sub>2</sub> are each independently hydrogen, alkyl, arylalkyl, aryl, alkoxy, hydroxyalkyl, hydroxyalkoxy,



15      wherein G is NH<sub>2</sub>, NCS,  $\begin{matrix} O \\ || \\ N-C-CH_2-X \end{matrix}$ , CO<sub>2</sub>H, NHR<sub>4</sub>,

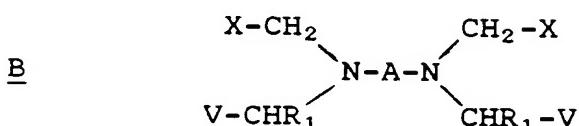
N(R<sub>4</sub>)<sub>2</sub>, CN, wherein R<sub>4</sub> is alkyl or hydroxyalkyl,



30      wherein n and m are zero or an integer from one to five, R<sub>3</sub> is hydrogen, hydroxyalkyl, alkoxy, alkyl, aryl, arylalkyl or hydroxyalkoxy and X is chloro, bromo or iodo.

5. The excipient of claim 1 wherein L and L' are independently selected from the compounds of the formula

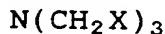
5



10

or

10

C

wherein

X is -COOY, PO<sub>3</sub>HY or -CONHOY;

15 Y is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A is -CHR<sub>2</sub>-CHR<sub>3</sub>-, -CH<sub>2</sub>CH<sub>2</sub>(ZCH<sub>2</sub>-CH<sub>2</sub>)<sub>m</sub>-,

20  $\begin{array}{c} \text{N}(\text{CH}_2\text{X})_2 \\ | \\ -\text{CH}_2-\text{CH}-\text{CH}_2 \end{array}$ , or  $\begin{array}{c} \text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{X})_2 \\ | \\ -\text{CH}_2-\text{CH}_2-\text{N}-\text{CH}_2-\text{CH}_2- \end{array}$ , wherein X is as defined above;

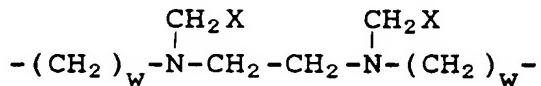
each R<sub>1</sub> is hydrogen or methyl;

25 R<sub>2</sub> and R<sub>3</sub> together represent a trimethylene group or a tetramethylene group or individually are hydrogen atoms, lower alkyl groups (e.g., 1-8 carbons), phenyl groups, benzyl groups or R<sub>2</sub> is a hydrogen atom and R<sub>3</sub> is -(CH<sub>2</sub>)<sub>p</sub>-C<sub>6</sub>H<sub>4</sub>-W-protein where p is 0 or 1, W is -NH-, -NHCOCH<sub>2</sub>- or -NHCS-, protein represents a protein residue;

30 m is 1, 2 or 3;

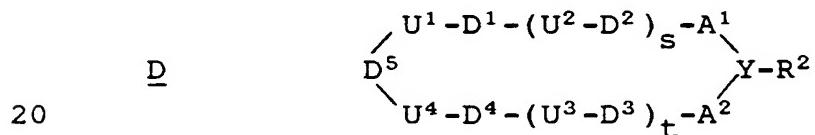
Z is an oxygen atom or a sulfur atom or the group NCH<sub>2</sub>X or NCH<sub>2</sub>CH<sub>2</sub>OR<sub>4</sub> wherein X is as defined above and R<sub>4</sub> is C<sub>1-8</sub>alkyl;

V is X or is -CH<sub>2</sub>OH, -CONH(CH<sub>2</sub>)<sub>n</sub>X or -COB,  
 wherein X is as defined above, B is a protein or  
 lipid residue, n is an integer from 1 to 12, or if  
 R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are each hydrogen; then both V's  
 5 together form the group



10 where X is as above, w is 1, 2 or 3, provided that  
 at least two of the substituents Y represent metal  
 ion equivalents of an element with an atomic number  
 of 21 to 29, 42, 44 or 57 to 83.

15 6. The excipient of claim 1 wherein L and  
 L' are independently selected from the compounds of  
 the formula



wherein

Y is N or P;

25 A<sup>1</sup> and A<sup>2</sup> are each optionally branched C<sub>2-6</sub>  
 alkylene;

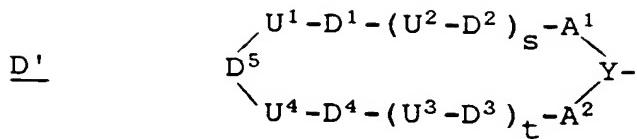
U<sup>1</sup>, U<sup>2</sup>, U<sup>3</sup> and U<sup>4</sup> are each a single bond or  
 optionally branched C<sub>1-6</sub> alkylene;

D<sup>1</sup>, D<sup>2</sup>, D<sup>3</sup>, D<sup>4</sup> are each O, S, C<sub>1-6</sub> alkylene  
 or NR<sub>7</sub>;

30 R<sub>7</sub> is hydrogen or C<sub>1-4</sub> alkylene having a  
 COOR<sup>1</sup> terminal group;

R<sup>1</sup> is hydrogen or a metal ion equivalent;

- D<sup>5</sup> is D<sup>1</sup> or CHR<sup>5</sup>, where R<sup>5</sup> can be hydrogen or optionally unsaturated C<sub>1-20</sub> alkylene which may include imino, phenyleneoxy, phenyleneimino, amido, ester, O, S and/or N optionally substituted with OH, SH imino and/or amino and may carry a terminal functional group (optionally bonded to a macromolecule B);
- s and t are each 0-5;
- R<sub>2</sub> is hydrogen, optionally substituted C<sub>1-16</sub> alkyl, acyl, acylalkyl (optionally substituted by one or more OH or lower alkoxy groups), -CH<sub>2</sub>-X-V, B or CH<sub>2</sub>COB where X is CO, optionally branched C<sub>1-10</sub> alkylene (optionally substituted by 1 or more OH or lower alkoxy groups) or optionally branched C<sub>2-23</sub> alkylene interrupted by O;
- V is NR<sup>3</sup>R<sup>4</sup> or COOR<sup>6</sup>;
- R<sup>3</sup> and R<sup>4</sup> are each hydrogen, C<sub>1-16</sub> alkyl (optionally substituted by 1 or more OH or lower alkoxy groups) or together complete a 5-6 membered heterocycle optionally containing another heteroatom;
- R<sub>6</sub> is hydrogen, C<sub>1-16</sub> saturated, unsaturated, linear branched or cyclic hydrocarbyl, aryl or aralkyl;
- R<sub>2</sub> or R<sub>3</sub> can be bonded by a C<sub>2-20</sub> alkylene chain (optionally having a terminal carbonyl group, optionally interrupted by 1 or more O or R<sup>1</sup> carboxymethylimino, or substituted by one or more OH, lower alkoxy or carboxy lower alkyl groups) to a second macromolecule of the formula



5 which second macromolecule D' can be the same as or different from the macromolecule of D.

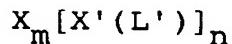
7. The excipient of claim 1 wherein L and L' are independently selected from 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, 1,4,7-tris-(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane,  
 10 N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine, DTPA-bis methylamide, DTPA bis morpholinoamide and DTPA bis 1,2-dihydroxypropylamide.

15 8. The excipient of claim 1 wherein L and L' are the same organic ligand.

9. A contrast agent composition for use in magnetic resonance, x-ray, ultrasound and radio-diagnostic imaging comprising

20 a metal ion, M, complexed with an organic ligand, L;

a complex salt excipient of the formula



25 wherein X and X' are each independently selected from calcium or zinc, L' is an organic ligand which may be L or another organic ligand which has a greater affinity for M than for calcium or zinc,  
 30 and wherein m and n are each independently 1, 2 or 3; and,

a pharmaceutically acceptable carrier therefor.

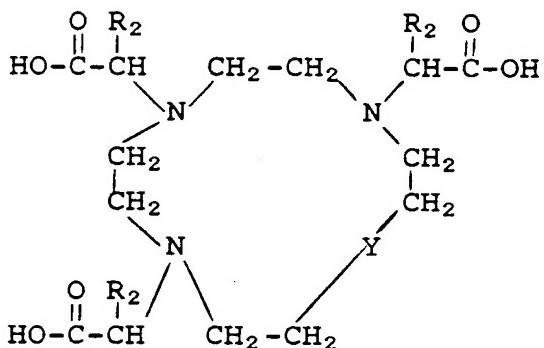
10. The composition of claim 9 where X and X' are each calcium.

11. The composition of claim 9 wherein L and L' are independently selected from linear and  
5 macrocyclic polyaminopolycarboxylic acids and derivatives thereof.

12. The composition of claim 9 wherein L and L' are independently selected from compounds of the formula

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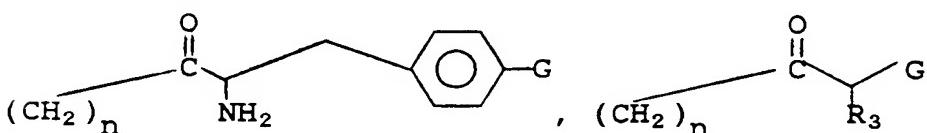
wherein

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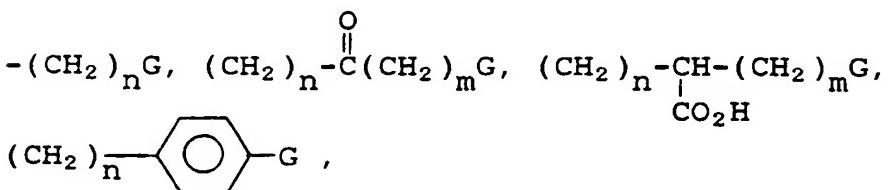
Y is oxygen or  $\overset{R_1}{\underset{|}{\text{N}}}$ ;

R<sub>1</sub> and R<sub>2</sub> are each independently hydrogen, alkyl, arylalkyl, aryl, alkoxy, hydroxyalkyl, hydroxyalkoxy,

25

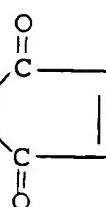


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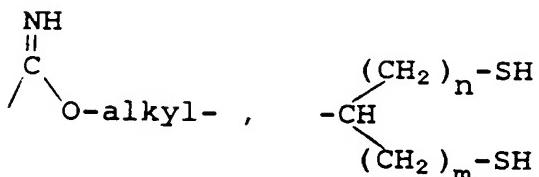


wherein G is NH<sub>2</sub>, NCS,  $\text{N}(\text{C}-\text{CH}_2-\text{X})$ , CO<sub>2</sub>H, NHR<sub>4</sub>,  
 N(R<sub>4</sub>)<sub>2</sub>, CN, wherein R<sub>4</sub> is alkyl or hydroxyalkyl,

5

hydroxyalkoxy, -N(R)-,  (where A is

10



an anion),

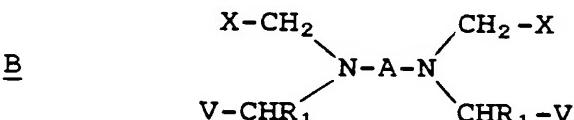
15

wherein n and m are zero or an integer from one to five, R<sub>3</sub> is hydrogen, hydroxyalkyl, alkoxy, alkyl, aryl, arylalkyl or hydroxyalkoxy and X is chloro, bromo or iodo.

20

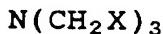
13. The composition of claim 9 wherein L and L' are independently selected from the compounds of the formula

25



or

30

C

wherein

X is -COOY, PO<sub>3</sub>HY or -CONHOY;

Y is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A is  $-\text{CHR}_2-\text{CHR}_3-$ ,  $-\text{CH}_2\text{CH}_2(\text{ZCH}_2-\text{CH}_2)_m-$ ,

5            $\text{N}(\text{CH}_2\text{X})_2$                                     $\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{X})_2$   
 $-\text{CH}_2-\overset{\text{l}}{\underset{\text{CH}-\text{CH}_2}{\text{C}}}-\text{CH}_2$  , or  $-\text{CH}_2-\text{CH}_2-\overset{\text{l}}{\underset{\text{N}-\text{CH}_2-\text{CH}_2-}{\text{C}}}-$  , wherein  
X is as defined above;

each R<sub>1</sub> is hydrogen or methyl;

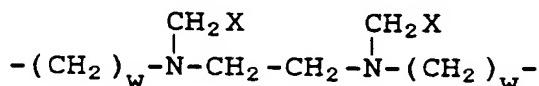
10           R<sub>2</sub> and R<sub>3</sub> together represent a trimethylene group or a tetramethylene group or individually are hydrogen atoms, lower alkyl groups (e.g., 1-8 carbons), phenyl groups, benzyl groups or R<sub>2</sub> is a hydrogen atom and R<sub>3</sub> is  $-(\text{CH}_2)_p-\text{C}_6\text{H}_4-\text{W-protein}$  where p is 0 or 1, W is -NH-, -NHCOCH<sub>2</sub>- or -NHCS-, protein represents a protein residue;

15           m is 1, 2 or 3;

20           Z is an oxygen atom or a sulfur atom or the group NCH<sub>2</sub>X or NCH<sub>2</sub>CH<sub>2</sub>OR<sub>4</sub> wherein X is as defined above and R<sub>4</sub> is C<sub>1-8</sub>alkyl;

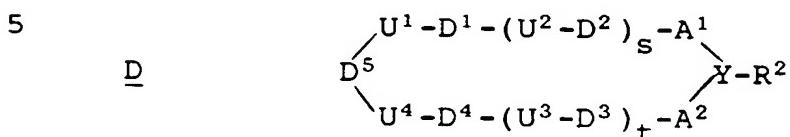
25           V is X or is  $-\text{CH}_2\text{OH}$ ,  $-\text{CONH}(\text{CH}_2)_n\text{X}$  or  $-\text{COB}$ , wherein X is as defined above, B is a protein or lipid residue, n is an integer from 1 to 12, or if R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are each hydrogen; then both V's together form the group

25



30           where X is as above, w is 1, 2 or 3, provided that at least two of the substituents Y represent metal ion equivalents of an element with an atomic number of 21 to 29, 42, 44 or 57 to 83.

14. The composition of claim 9 wherein L and L' are independently selected from the compounds of the formula



wherein

10 Y is N or P;

$A^1$  and  $A^2$  are each optionally branched  $C_{2-6}$  alkylene;

$U^1$ ,  $U^2$ ,  $U^3$  and  $U^4$  are each a single bond or optionally branched  $C_{1-6}$  alkylene;

15            $D^1$ ,  $D^2$ ,  $D^3$ ,  $D^4$  are each O, S, C<sub>1-6</sub> alkylene  
or NR<sub>7</sub>;

R<sub>7</sub> is hydrogen or C<sub>1-4</sub> alkylene having a COOR<sup>1</sup> terminal group;

$R^1$  is hydrogen or a metal ion equivalent;

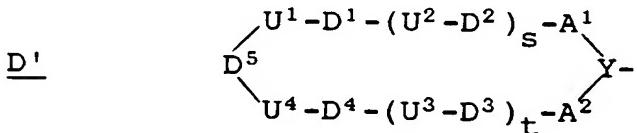
20           D<sup>5</sup> is D<sup>1</sup> or CHR<sup>5</sup>, where R<sup>5</sup> can be hydrogen  
or optionally unsaturated C<sub>1-20</sub> alkylene which may  
include imino, phenyleneoxy, phenyleneimino, amido,  
ester, O, S and/or N optionally substituted with  
OH, SH imino and/or amino and may carry a terminal  
25 functional group (optionally bonded to a  
macromolecule B):

s and t are each 0-5:

30        R<sub>2</sub> is hydrogen, optionally substituted C<sub>1-16</sub> alkyl, acyl, acylalkyl (optionally substituted by one or more OH or lower alkoxy groups), -CH<sub>2</sub>-X-V, B or CH<sub>2</sub>COB where X is CO, optionally branched C<sub>1-10</sub> alkylene (optionally substituted by 1 or more OH or lower alkoxy groups) or optionally branched C<sub>2-23</sub> alkylene interrupted by O;

V is NR<sup>3</sup>R<sup>4</sup> or COOR<sup>6</sup>;

- R<sup>3</sup> and R<sup>4</sup> are each hydrogen, C<sub>1-16</sub> alkyl (optionally substituted by 1 or more OH or lower alkoxy groups) or together complete a 5-6 membered heterocycle optionally containing another heteroatom;
- 5 R<sub>6</sub> is hydrogen, C<sub>1-16</sub> saturated, unsaturated, linear branched or cyclic hydrocarbyl, aryl or aralkyl;
- 10 R<sub>2</sub> or R<sub>3</sub> can be bonded by a C<sub>2-20</sub> alkylene chain (optionally having a terminal carbonyl group, optionally interrupted by 1 or more O or R<sup>1</sup> carboxymethylimino, or substituted by one or more OH, lower alkoxy or carboxy lower alkyl groups) to
- 15 a second macromolecule of the formula



which second macromolecule D' can be the same as or different from the macromolecule of D.

15. The composition of claim 9 wherein L and L' are independently selected from 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane, N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine, DTPA bis methylamide, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DTPA bis morpholinoamide and DTPA bis 1,2-dihydroxypropylamide.

16. The composition of claim 9 wherein L and L' are the same organic ligand.

17. The composition of claim 9 wherein the mole ratio of said complex salt to said metal chelate contrast agent is between about 0.05 and 10 percent.

18. The composition of claim 9 wherein said metal ion is selected from paramagnetic metal atoms, lanthanide series elements, yttrium, and the transition series elements.

19. The composition of claim 18 wherein said paramagnetic metals are selected from gadolinium(III), dysprosium(III), manganese(II), manganese(III), chromium(III), iron(II) and iron(III).

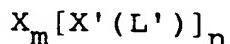
20. The composition of claim 9 wherein said metal ion complexed with an organic ligand is gadolinium(III) 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane and said excipient is calcium bis[1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraaza-cyclododecanatocalcium(II)].

21. The composition of claim 9 wherein said metal ion complexed with an organic ligand is N-methylglucamine gadolinium (III) 1,4,7,10-tetra-azacyclododecane-N,N',N'',N'''-tetraacetic acid and said excipient is calcium [1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetraacetatocalcium(II)].

22. The composition of claim 9 wherein said metal ion complexed with an organic ligand is di-N-methylglucaminium gadolinium(III) N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine and said excipient is calcium bis[diethylenetriamine-N,N',N'',N'''-pentaacetatocalcium(II)].

23. The composition of claim 9 wherein said metal ion complexed with an organic ligand is diethylene triamine pentaacetato-bis methylamide-gadolinium(III) and said excipient is calcium bis[diethylenetriamine-N,N'N',N'',N''-pentaacetato-bis methylamide-calcium(II)].
- 5       24. The composition of claim 9 wherein said metal ion complexed with an organic ligand is gadolinium(III) 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid and said excipient is calcium bis[1,4,7,10-tetraazacyclododecane-1,4,7-triacetato-calcium(II)].
- 10      25. The composition of claim 9 wherein said metal ion complexed with an organic ligand is gadolinium (III) DTPA bis morpholinoamide and said excipient is calcium bis [DTPA-bis morpholinamido calcium (II)].
- 15      26. The composition of claim 9 wherein said metal ion complexed with an organic ligand is gadolinium (III) DTPA bis 1,2-dihydroxypropylamide and said excipient is calcium bis[DTPA bis 1,2-dihydroxypropylamido calcium (II)].
- 20      27. A contrast agent composition comprising a metal chelate which is gadolinium (III) 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane; an excipient which is calcium bis[1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecanatocalcium(II)];
- 25      30     a buffer; acidic and/or basic solution sufficient to adjust pH of said composition to a desired value; and water.

28. In a method of diagnostic imaging which employs an agent comprising a metal ion, M, complexed with an organic ligand, L, and a pharmaceutically acceptable carrier therefor, the  
 5 improvement wherein said agent further includes an excipient of the formula



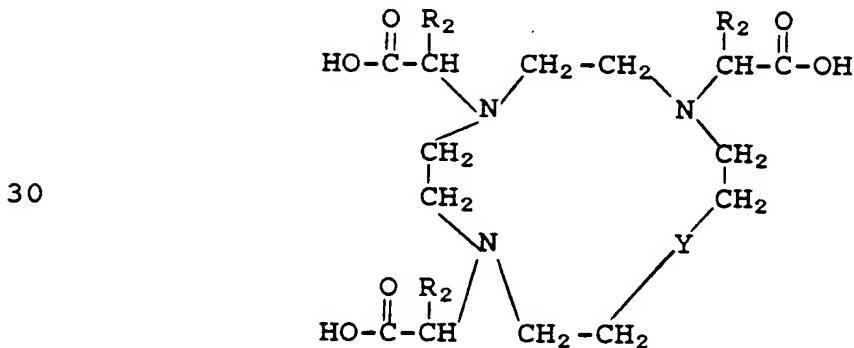
10 wherein X and X' are each independently selected from calcium or zinc, L' is an organic ligand which may be L or another organic ligand which has a greater affinity for M than for calcium or zinc, and wherein m and n are each independently 1, 2 or  
 15 3.

29. The method of claim 28 wherein X and X' are each calcium.

30. The method of claim 28 wherein L and L' are independently selected from linear and  
 20 macrocyclic polyaminopolycarboxylic acids and derivatives thereof.

31. The method of claim 28 wherein L and L' are independently selected from compounds of the formula

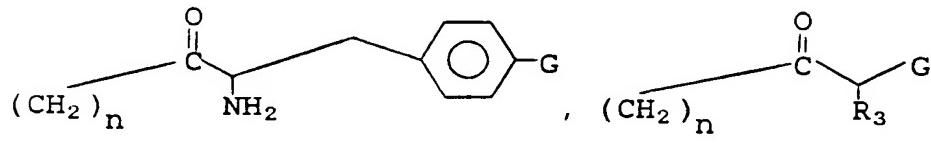
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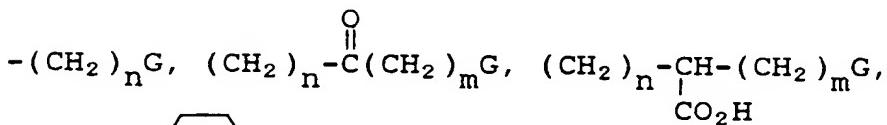
wherein

$\text{Y}$  is oxygen or  $-\overset{\text{R}_1}{\underset{|}{\text{N}}}-$ ;

- 5       $\text{R}_1$  and  $\text{R}_2$  are each independently hydrogen, alkyl, arylalkyl, aryl, alkoxy, hydroxyalkyl, hydroxyalkoxy,



10



15

wherein  $\text{G}$  is  $\text{NH}_2$ ,  $\text{NCS}$ ,  $\text{N}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-\text{CH}_2-\text{X}$ ,  $\text{CO}_2\text{H}$ ,  $\text{NHR}_4$ ,

$\text{N}(\text{R}_4)_2$ ,  $\text{CN}$ , wherein  $\text{R}_4$  is alkyl or hydroxyalkyl,

20

hydroxyalkoxy,  $-\text{N}\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ | \\ \text{C} \\ \parallel \\ \text{O} \end{array}\right)$ ,  $\text{C}_6\text{H}_5-\text{N}_2^+\text{A}^-$  (where  $\text{A}$  is

25

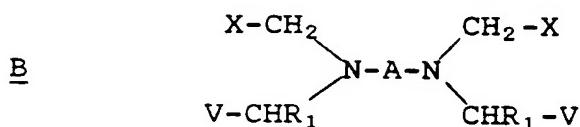
an anion),  $\text{O-alkyl-}$ ,  $-\text{CH}\left(\begin{array}{c} (\text{CH}_2)_n-\text{SH} \\ | \\ (\text{CH}_2)_m-\text{SH} \end{array}\right)$ ,

30

wherein  $n$  and  $m$  are zero or an integer from one to five,  $\text{R}_3$  is hydrogen, hydroxyalkyl, alkoxy, alkyl, aryl, arylalkyl or hydroxyalkoxy and  $\text{X}$  is chloro, bromo or iodo.

32. The method of claim 28 wherein L and L' are independently selected from the compounds of the formula

5



or

10



wherein

X is -COOY, PO<sub>3</sub>HY or -CONHOY;

15 Y is a hydrogen atom, a metal ion equivalent and/or a physiologically biocompatible cation of an inorganic or organic base or amino acid;

A is -CHR<sub>2</sub>-CHR<sub>3</sub>- , -CH<sub>2</sub>CH<sub>2</sub>(ZCH<sub>2</sub>-CH<sub>2</sub>)<sub>m</sub>- ,

20  $\begin{array}{ccc} \text{N}(\text{CH}_2\text{X})_2 & & \text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_2\text{X})_2 \\ | & & | \\ -\text{CH}_2-\text{CH}-\text{CH}_2 & , \text{ or } & -\text{CH}_2-\text{CH}_2-\text{N}-\text{CH}_2-\text{CH}_2- \end{array}$ , wherein  
X is as defined above;

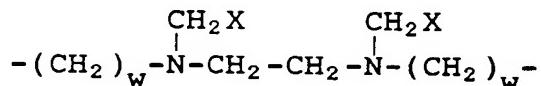
each R<sub>1</sub> is hydrogen or methyl;

25 R<sub>2</sub> and R<sub>3</sub> together represent a trimethylene group or a tetramethylene group or individually are hydrogen atoms, lower alkyl groups (e.g., 1-8 carbons), phenyl groups, benzyl groups or R<sub>2</sub> is a hydrogen atom and R<sub>3</sub> is -(CH<sub>2</sub>)<sub>p</sub>-C<sub>6</sub>H<sub>4</sub>-W-protein where p is 0 or 1, W is -NH-, -NHCOCH<sub>2</sub>- or -NHCS-, protein represents a protein residue;

30 m is 1, 2 or 3;

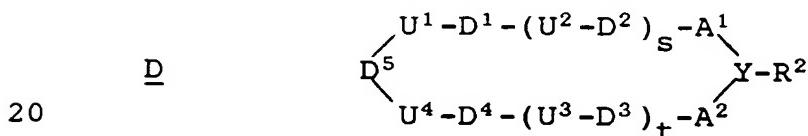
Z is an oxygen atom or a sulfur atom or the group NCH<sub>2</sub>X or NCH<sub>2</sub>CH<sub>2</sub>OR<sub>4</sub> wherein X is as defined above and R<sub>4</sub> is C<sub>1-8</sub>alkyl;

V is X or is -CH<sub>2</sub>OH, -CONH(CH<sub>2</sub>)<sub>n</sub>X or -COB,  
wherein X is as defined above, B is a protein or  
lipid residue, n is an integer from 1 to 12, or if  
R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are each hydrogen; then both V's  
5 together form the group



10 where X is as above, w is 1, 2 or 3, provided that at least two of the substituents Y represent metal ion equivalents of an element with an atomic number of 21 to 29, 42, 44 or 57 to 83.

33. The method of claim 28 wherein L and L'  
15 are independently selected from the compounds of  
the formula



wherein

Y is N or P;

A<sup>1</sup> and A<sup>2</sup> are each optionally branched C<sub>2-6</sub> alkylene;

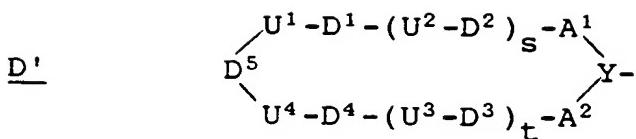
$U^1$ ,  $U^2$ ,  $U^3$  and  $U^4$  are each a single bond or optionally branched C<sub>-6</sub> alkylene;

$D^1$ ,  $D^2$ ,  $D^3$ ,  $D^4$  are each O, S,  $C_{1-6}$  alkylene or  $NR_2$ ;

30 R<sub>7</sub> is hydrogen or C<sub>1-4</sub> alkylene having a COOR<sup>1</sup> terminal group:

$R^1$  is hydrogen or a metal ion equivalent:

- D<sup>5</sup> is D<sup>1</sup> or CHR<sup>5</sup>, where R<sup>5</sup> can be hydrogen or optionally unsaturated C<sub>1-20</sub> alkylene which may include imino, phenyleneoxy, phenyleneimino, amido, ester, O, S and/or N optionally substituted with
- 5 OH, SH imino and/or amino and may carry a terminal functional group (optionally bonded to a macromolecule B);
- s and t are each 0-5;
- R<sub>2</sub> is hydrogen, optionally substituted C<sub>1-16</sub> alkyl, acyl, acylalkyl (optionally substituted by one or more OH or lower alkoxy groups), -CH<sub>2</sub>-X-V, B or CH<sub>2</sub>COB where X is CO, optionally branched C<sub>1-10</sub> alkylene (optionally substituted by 1 or more OH or lower alkoxy groups) or optionally branched C<sub>2-23</sub>
- 10 alkylene interrupted by O;
- 15 V is NR<sup>3</sup>R<sup>4</sup> or COOR<sup>6</sup>;
- R<sup>3</sup> and R<sup>4</sup> are each hydrogen, C<sub>1-16</sub> alkyl (optionally substituted by 1 or more OH or lower alkoxy groups) or together complete a 5-6 membered
- 20 heterocycle optionally containing another heteroatom;
- R<sub>6</sub> is hydrogen, C<sub>1-16</sub> saturated, unsaturated, linear branched or cyclic hydrocarbyl, aryl or aralkyl;
- 25 R<sub>2</sub> or R<sub>3</sub> can be bonded by a C<sub>2-20</sub> alkylene chain (optionally having a terminal carbonyl group, optionally interrupted by 1 or more O or R<sup>1</sup> carboxymethylimino, or substituted by one or more OH, lower alkoxy or carboxy lower alkyl groups) to
- 30 a second macromolecule of the formula



5 which second macromolecule D' can be the same as or different from the macromolecule of D.

34. The method of claim 28 wherein L and L' are independently selected from 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, 1,4,7-tris-(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane, N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine, DTPA-bis methylamide, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DTPA bis morpholinoamide and DTPA bis 1,2-dihydroxypropylamide.

35. The method of claim 28 wherein L and L' are the same organic ligand.

36. The method of claim 28 wherein the mole ratio of said complex salt to said metal chelate contrast agent is between about 0.05 and 10 percent.

37. The method of claim 28 wherein said metal ion is selected from paramagnetic metal atoms, lanthanide series elements, yttrium, and the transition series elements.

38. The method of claim 28 wherein said paramagnetic metals are selected from gadolinium(III), octahedral manganese(II), chromium(III), and iron(III).

39. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium(III) 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane and  
5 said excipient is calcium bis[1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraaza-cyclododecanatocalcium(II)].

40. The method of claim 28 wherein said metal ion complexed with an organic ligand is  
10 N-methylglucamine gadolinium (III) 1,4,7,10-tetra-azacyclododecane-N,N',N",N'''-tetraacetic acid and said excipient is calcium [1,4,7,10-tetraazacyclo-dodecane-1,4,7,10-tetraacetatocalcium(II)].

41. The method of claim 28 wherein said  
15 metal ion complexed with an organic ligand is di-Nmethylglucamine gadolinium(III) N,N-bis[2-[bis-(carboxymethyl)-amino]ethyl]glycine and said excipient is calcium bis[diethylenetriamine-N,N',N',N",N"-pentaacetatocalcium(II)].

20 42. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium(III) N,N-bis[2-[bis(carboxymethyl)-amino]ethyl]glycine-bis methylamide and said  
excipient is calcium bis[diethylenetriamine-N,N',N",N"-pentaacetato-bis methylamide-  
25 calcium(II)].

43. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium(III) 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid and said excipient is calcium bis[1,4,7,10-tetraazacyclododecane-1,4,7-triacetato-calcium(II)].

5           44. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium (III) DTPA bis morpholinoamide and said 10 excipient is calcium bis [DTPA-bis morpholinamido calcium (II)].

15           45. The method of claim 28 wherein said metal ion complexed with an organic ligand is gadolinium (III) DTPA bis 1,2-dihydroxypropylamide and said excipient is calcium bis[DTPA bis 1,2-dihydroxypropylamido calcium (II)].

20           46. The method of claim 28 wherein said contrast agent composition comprising  
              a metal chelate which is gadolinium (III)  
              1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-  
              1,4,7,10-tetraazacyclododecane;  
              an excipient which is calcium bis[1,4,7-  
              tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-  
              tetraazacyclododecanatocalcium(II)];  
25           a buffer;  
              acidic and/or basic solution sufficient to  
              adjust pH of said composition to a desired value;  
              and  
              water.